REMARKS

Claims 4-5, 10-13 and 15-27 are pending the application; Claims 4-5, 10-13 and 15-23 stand rejected. Claims 24-27 are withdrawn. By this Amendment Claims 24-27 have been cancelled without prejudice and Claims 4, 10, 11, 22 and 23 have been amended. These amendments add no new matter to the application.

Claims 4, 5 and 10 stand rejected under 35 USC 112 as allegedly indefinite; Applicant respectfully traverses these rejections. However in the interest of arriving at an early indication of allowable subject matter, claim 4 (from which claims 5 and 10 depend) has been amended to remove the reference to "other amyloidoses". Applicant also traverses the Examiner's position that "plant materials" in claim 10 lacks antecedent basis; this expression is not preceded by a definite article, so as thus to trigger an antecedent concern, but rather is preceded by the well-known substitute "one or more" for the indefinite article "a". However in the interest of arriving at an early indication of allowable subject matter, claim 10 has been amended to change the reference from "one or more plant materials" to --a plant material--. These claims are therefore believed to be in condition for allowance and reconsideration is requested.

Claims 22 and 23 stand rejected under 35 USC 112 as allegedly indefinite; Applicant respectfully traverses these rejections. Claims 22-23 are directed to the use of a source of green tea, green tea leaves or green tea leaf extract in the preparation of various pharmaceutical compositions or dietary supplements; the process step of using the green tea in the preparation of the products is implicit, and Applicant does not believe that it requires being made explicit; however in the interest of arriving at an early indication of allowable subject matter, Claims 22 and 23 are amended to explicitly state a process step, and they are now believed to be in condition for allowance, and reconsideration is requested.

Claims 4-5, 10-12, 19 and 21 stand rejected un 35 USC 112 as allegedly not enabled; Applicant respectfully traverses these rejections. Applicant respectfully asserts that the Examiner's reliance *In re Wands* in the enablement argument is misplaced or misapplied. Contrary to the Examiner's assertion that the specification does not teach the skilled artisan how

to prevent amyloid fibril formation, Applicant respectfully submits that that is just what the specification does do. It does so by teaching the artisan how to prepare compositions for, and methods for, administering to mammals and patients and the like various combinations of the claimed substances, such as epicatechin and green tea extracts.

It appears that the Examiner's current assessment of the specification has been inappropriately limited to only four to the eight *Wands* factors, and of those four, several appear to have been incorrectly applied. One of the factors not currently addressed is the factor of quantity of experimentation needed to effect the application of the claimed subject matter. Earlier, the Examiner had argued that there would be an undue amount of experimentation necessary to effect the claimed methodologies; but Applicant rebutted this position, saying, "method claims at issue all clearly state their mode of employment, and no experimentation at all is required to practice the invention as variously claimed, it being well accepted by those skilled in the art that determination of appropriate therapeutically effective amounts of claimed compositions is not considered to be experimentation. This is particularly true when, as is presented in this case, the efficacy of the disclosed embodiments is so great in general as to render practically any amount of any of the disclosed embodiments at least minimally therapeutically effective." To this rebuttal the Examiner has now apparently acquiesced, as there is no further discussion of quantity of experimentation as an issue in the patentability of these claims. This first *Wands* factor therefore may be presumed to weigh in Applicant's favor.

The other factors not addressed are: amount of direction and guidance provided, relative skill of those in the art, and breadth of the claims. All of these factors as well weigh in Applicants favor. The specification does provide adequate guidance and direction, particularly in view of the well-known high level of skill of others in the art; the specification more than sufficiently teaches those skilled in the art how to use the claimed substances to achieve the claimed therapeutic effects. The claims are not too broad, and in some respects at least are quite particular. All of these four favorable factors must be evaluated as well in determining enablement, not just the four factors currently selected by the Examiner.

As to the first such factor, nature of the invention, the Examiner does no more than recite, in abbreviated form, the preamble to the claims which in general is directed to methods "for the treatment, inhibition, prevention or management of amyloid fibril formation, deposition, accumulation, aggregation and/or persistence in Alzheimer's disease and type II diabetes".[1] The Examiner makes no discussion of any alleged deficiency or negative effect in these recitation of the nature of the claims.

As to the second factor, state of the prior art, Applicant must respectfully traverse the Examiner's characterization that the state of the art would suggest to the skilled artisan that successful treatment as claimed would be "highly unlikely". First of all, Applicant is aware of no such implications throughout the entire body of literature in the art, and significantly, the Examiner has cited no support in the literature for this position. The Examiner has an affirmative duty to support such statements, and has not done so here. The state of the art is actually such that there is no prior discussion whatever about the claimed therapeutic methods. This is not surprising in view of Applicant's claim to have invented these methods; naturally, there would be no previous discussions in the art. However, an absence of earlier discussion of claimed subject matter in the art cannot be taken as a negative indication as to likelihood of success of the claimed methods, otherwise all new methods would be so negatively regarded and all of them would fail to pass patentability muster. Secondly, the very substance of the specification is all to the effect of the success of the claimed methods, and the Examiner has shown nothing to the contrary.

As to the third factor, predictability, Applicant must respectfully also traverse the Examiner's characterization that the skilled artisan would view the claimed methods as "highly unpredictable". Applicant does not believe that this is correct; but more importantly, this is not a correct application of this factor. Predictability as discussed in *Wands* relates to the predictability of the parameters of the particular claimed step, not to the predictability of the

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[1] Actually, and significantly, several of the rejected claims are not at all directed to Alzheimer's disease, but rather to α-synuclein fibril formation and the like in Parkinson's disease and other α-synuclein diseases (11-12), and to reducing, disrupting, dissolving, inhibiting, eliminating or preventing in a patient one or more conditions involving: the brain (19) or the pancreas (21). How the Examiner's rejections apply to these latter claims is not at all clear to Applicant, and Applicant believes that these claims may in fact not be included in the rejection at all, such that they are otherwise currently in condition for allowance.

outcome or success of the claimed method as a whole; again, no new invention will prove to be initially very predictable in its effect and success, and such predictability has never been a factor in evaluating patentability, beyond a bare threshold determination that the claimed invention passes section 101 requirements of operability. And the Examiner does not here allege that the claimed invention is inoperable. Rather, the prior art is replete with examples of how those skilled in the art may readily predict just how much of a given substance will be needed to achieve a therapeutic effect, within the context of the various claimed subject matters. This factor therefore also weighs decidedly in Applicant's favor.

As to the fourth factor, working examples, the Examiner merely repeats that there are "**no** working examples [Examiner's emphasis]" perhaps, in such emphasis, actually suggesting that this is still the only factor that the Examiner is concerned with. Applicant respectfully asserts that working examples are never a statutory requirement in such a specification, and that in this particular case none are at all needed in order for the skilled artisan to be able to put the claimed invention readily into practice. And beyond cited the apparent lack of working examples, the Examiner has not shown anything of substance to suggest the contrary. Applicant submits that it is abundantly clear to the skilled artisan that the claims all set forth a mode of employment, and no experimentation would be required to practice the claimed invention.

Applicant urges the Examiner to consider, along with other factors, that it is Applicant alone who has originally discovered and disclosed for the public benefit the efficacy of the various claimed substances for treating amyloidoses, and amyloid and alpha-synuclein fibrillogenesis, and is alone entitled under the law to claims of commensurate scope with this discovery and disclosure. Applicant urges the Examiner to consider that it is the policy underlying the law that the public be bettered by so encouraging just this kind of discovery and disclosure with the issuance of patent grants.

Claims 4-5, 10-13 and 15-21 stand rejected under 35 USC §102 as allegedly anticipated by Castillo WO 98/51302; Applicant respectfully traverses these rejections. Amended claims 4 and 11 now require selection of a therapeutic substance that can only be either green tea, green

tea leaves, green tea extract or epicatechin, and claims 13 and 15-21 require the use of epicatechin. Castillo does not make any mention of these substances at all, much less as efficacious in anti-fibrillogenesis. Castillo thus does not anticipate claims 4-5, 10-13 or 15-21. In addition, Claim 10 depends from claim 4 and properly construed contains all the limitation of claim 4, and is therefore not anticipated either; moreover, claim 10 further requires the presence of at least one of the substances, ginkgo biloba, rosemary, gotu kola, bacopin or ginseng, and Castillo makes no mention whatever of these substances. Applicant traverses that Uncaria tomentosa is well known to contain epicatechin; Applicant submits that it is Applicant who is the first to have identified the presence of epicatechin in Uncaria tomentosa. These claims are therefore all believed to be allowable over Castillo, and reconsideration is requested.

Claims 4-5, 10-13 and 15-21 stand rejected under 35 USC §102 as allegedly anticipated by JP 10245342 (Mitsui Norin), and also by Shin-Ya; Applicant respectfully traverses these rejections. Independent claims 4 and 11 require either green tea, green tea leaves, green tea extract or epicatechin, and claims 13 and 15-21 require the use of epicatechin. Mitsui Norin and Shin-Ya do not make any mention of fibril formation at all, and certainly teach nothing whatever about alpha-synuclein fibril formation, nor anything about the other therapeutic targets claimed in claims 13-21. Mitsui Norin and Shin-Ya are narrow teachings directed only to nerve cell toxicity supposedly caused by beta-amyloid protein possibly being reduced with tea polyphenols, and to nerve cell death being induced by active oxygen . (See also Rule 132 Declaration of Dr. Alan Snow filed herewith.)

It appears that Examiner implies that Aß nerve cell toxicity NECESSARILY (that is, 'inherently') teaches an effect on inhibition of Aß fibril formation, deposition, accumulation and/or persistence. Dr. Snow states that he does not believe the literature supports such an implication, for reasons as detailed below.

At least one study by Wang (Wang, The Neuroprotective Effects of Phytoestrogens on Amyloid ß Protein-induced Toxicity Are Mediated by Abrogating the Activation of Caspase Cascade in Rat Cortical Neurons, J. Biological Chem., vol 276 no 7, pp 5287-5295, February

16, 2001) (copy attached to Snow Decl. for Examiner's ready reference) reports that "although Aß mediated neurotoxicity [is a] focus of intense interest, the underlying mechanisms are still controversial" (see p 5294, col 2 below fig. 9). Thus, there can be no necessary inference to be drawn from any study of Aß mediated neurotoxicity.

Wang also reports that nerve cell death or neurotoxicity is in fact the result of a cascade involving caspases and reactive oxygen species accumulation (see abstract p 5287 - near end). Also, Zhang (Zhang, Selective Cytotoxicity of Intracellular Amyloid ß Peptide 1-42 Through p53 and Bax in Cultured Primary Human Neurons, J. Cell Bio., vol 156 no 3, pp 519-529, February 3, 2002) (copy attached to Snow Decl. for Examiner's ready reference) reports that nonfibrilized and fibrilized Aß are equally toxic (see p 519, midway thru abstract), and corroborates Wang in suggesting a caspase cell death route (see p 525, col 1, 1st paragraph). This is further refutation that there is no necessary suggestion from any reported study that inhibition of Aß neurotoxicity will also lead to inhibition of Aß fibril formation, deposition, accumulation and/or persistence. There is likewise no suggestion in any of the literature that fibrillogenesis plays any part whatever in the reported cell death.

Wang even reports that the high antioxidant activity of flavanoids *per se* was not able to protect neurons against Aß-induced neurotoxicity (see p 5292, col 1, end of penultimate paragraph); thus teaching away from a suggestion that flavanoids might be useful in preventing Aß fibrillogenesis.

Thus there are no necessary inferences available as teachings to be applied to Aß fibrillogenesis from the cited studies pertaining to neuronal cell death, because in at least some of the reported studies, the causes of the cell death do not involve any effect on Aß fibrillogenesis. There is thus no implication available to serve as a teaching that inhibition of nerve cell death or nerve cell toxicity by Aß inherently leads to inhibition of Aß fibril formation, deposition, accumulation and/or persistence.

The teaching of the cited references is therefore not inherent in any of the rejected claims. It is submitted that the Examiner erroneously characterizes the Mitsui Norin reference when she

states that it discloses reduction of amyloidosis or amyloid formation, deposition or accumulation; in fact, Mitsui Norin makes no reference whatever to any of these processes. It is clear that Applicant is the only one disclosing reduction of amyloidosis or amyloid formation, deposition or accumulation through the use of selected therapeutic substances. Applicant respectfully submits that the cited doctrine of inherency therefore does not apply to the rejected method claims.

In addition, the Examiner cites *Ex parte Novitski* for authority as to rejections of claims for inherency; but *Novitski* is limited authority, and is not to the contrary of Applicant's claims in this case.[2] *Novitski* was a 1993 BPAI case where the Board affirmed rejection of a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia* because a patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition, but the Board concluded that nematode inhibition was an inherent property of the bacteria, the Board noting in particular that Novitski himself had stated in the specification that Wisconsin 526 possessed an 18% nematode inhibition rating. Thus [says the Board] Novitski himself had set up the inherency by disclosing a bacterial strain with nematode efficacy, and thereafter attempted to claim a method of using that strain or a similar strain against nematodes. [It is not known whether or not it was Novitski himself who had discovered the strain's nematode inhibition.]

Novitski is limited in authority because it is a BPAI case that was apparently not reviewed by a court, and because it is limited on its facts. In this case the facts are quite different. The cited references teach treatment of conditions with no necessary or inherent relationship between those conditions and the anti-fibrillogenic therapeutic targets of the rejected claims. Therefore *Novitski*, to the extent that it might be regarded as authority in this case, does not require rejection of the claims in this application.

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[2] The Examiner also cites MPEP section 2112.01 for further support of the inherency rejections in this latest office action; but MPEP section 2112.01 is strictly limited to composition and apparatus claims, not method claims, as are the only claims present in the application. Therefore, Applicant believes the Examiner intended to cite MPEP section 2112.02 Process Claims. It is this latter section that discusses the limited doctrine of inherency for method claims as embodied in *Novitski*, and Applicant responds accordingly.

The Examiner further cites the *Wiseman* case as support for inherency rejections. But the Federal Circuit has closely limited the holding of *Wiseman* case, saying,

> The Board relied on *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979), to support the Board's statement:
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> > If the claimed subject matter would have been obvious from the references, it is immaterial that the references do not state the problem or advantages ascribed thereto by appellant.
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> *Wiseman* does not support the generalization that the Board attributes to it. In *Wiseman* the prior art reference showed a similar problem and suggested a similar solution to that of the applicant. Specifically, the prior art showed a disc brake having grooves for the purpose of venting dust generated during use; the applicant showed a disc brake having grooves for the purpose of venting steam generated during use. The applicant asserted no results or properties that were not fairly suggested by the prior art. The court's discussion in *Wiseman* must be viewed in context, and as with all section 103 decisions, judgment must be brought to bear based on the facts of each case.

In re Randall Wright, 848 F.2d 1216, 6 USPQ2d 1959 (Fed.Cir. 1988). Thus *Wiseman* is limited by the Federal Circuit, and no generalization may be made by the Examiner as to materiality of differences between the teachings of cited references and the specific limitations of examined claims. The Court says all cases must be decided on their own facts. The Court also says, in reversing the PTO inherency rejection of claims,

> Thus the question is whether what the inventor did would have been obvious to one of ordinary skill in the art attempting to solve the problem upon which the inventor was working. *Rinehart*, 531 F.2d at 1054, 189 USPQ at 149; see also *In re Benno*, 768 F.2d 1340, 1346, 226 USPQ 683, 687 (Fed.Cir. 1985) ("appellant's problem" and the prior art "present different problems requiring different solutions").
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> The problem upon which Wright was working was improving the pitch-measuring capability of the level, not the visibility of the bubble. The PTO, having conceded that Wright's structure was unobvious for his intended purpose, erred in holding that this was not relevant. The problem solved by the invention is always relevant. The entirety of a claimed invention, including the combination viewed as a whole, the elements thereof, and the properties and purpose of the invention, must be considered. [Emphasis added]

Wright, 848 F.2d at 1219. As in the *Rinehart* and *Wright* cases, in this case, "[Applicant's] problem and the prior art present different problems requiring different solutions". It has to be relevant that the problem solved by Applicant (anti-fibrilogenesis, and various mental and pancreatic conditions) is not the problem addressed by the cited references (nerve cell toxicity and

cell death). The rejected claims are therefore not inherently present in the cited references, and they are therefore allowable over the cited art.

The specific limitations of the rejected claims must all be read in any attempt to read any of the claims upon any prior art methods, and the claimed methods differ markedly from the teachings of the cited references. The rejected claims are directed to a method of use of therapeutic quantities of disclosed substances to actually interfere with and prevent or reverse amyloid and alpha synuclein fibril and plaque formations, and to methods to cause the various salutary effects claimed in claims 13-21. The Examiner asserts that the cited references teach the same method steps that are claimed in this case, but that is not so, since each of the cited references has as its object the therapeutic treatment of a condition that is not the same condition as any of the targets of any of the rejected claims. In fact it is necessarily the case that, in the claimed method steps, the step of administering a therapeutic amount (or a therapeutically effective amount) of a selected substance is a step that is different from any implied step in any of the cited references, since whatever amount might be therapeutic in treating cell death or neurotoxicity (as taught by Shin-Ya and Mitsui Norin), is not necessarily therapeutic for any of the amyloid fibrillogenesis involved in the therapeutic targets of the rejected claims. (See again Snow Declaration.)

It is also fundamental to patent law that a brief and general reference to possible efficacy of a broad category of substances is not an anticipatory teaching as to the efficacy of any particular member of that category; at most it is a possible hint of a direction in which to research. Thus, a reference to tea polyphenols in general is not a teaching of the efficacy of any specific polyphenol. None of the cited references therefore teach the efficacy, in anti-fibrillogenic treatment of Alzheimer's and Parkinson's diseases or in any of the other therapeutic claims, of employing epicatechin or green tea as a therapeutic substance in a novel method of treatment. In passing, Applicant also traverses what the Examiner characterizes as an admission of prior art on page 5, lines 13-16 of the specification; Applicant discloses that catechins are present in green tea,

as part of Applicant's report of it's own discoveries, and does not therein admit that such knowledge was already prior art at the time of disclosure.

The rejected claims are therefore all believed to be allowable over the art of record, and reconsideration is requested.

Applicant believes that it has responded fully to all of the concerns expressed by the Examiner in the Office Action, and respectfully requests that reexamination of all rejected claims and early favorable action on them as well. If the Examiner has any further concerns, Applicant requests a call to Patrick Dwyer at (206) 343-7074.

Respectfully submitted,

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